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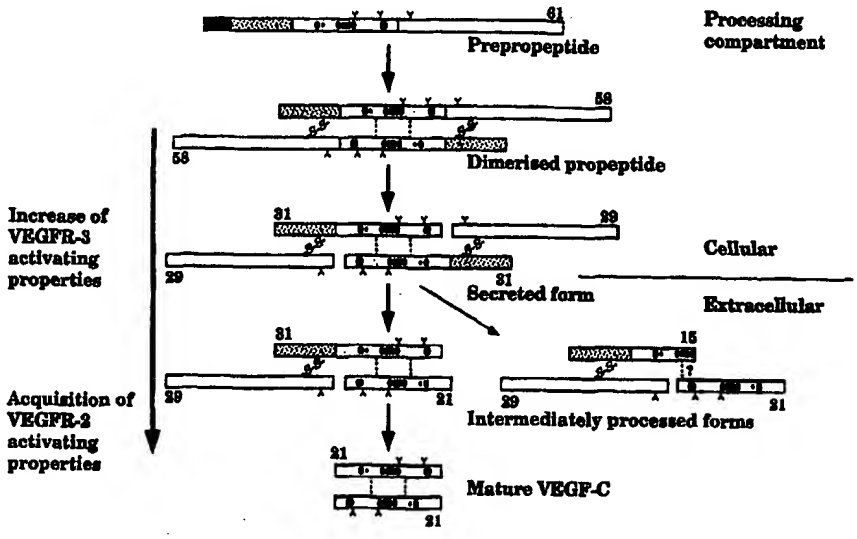
(54) Title: VASCULAR ENDOTHELIAL GROWTH FACTOR C (VEGF–C) PROTEIN AND GENE, MUTANTS THEREOF, AND USES THEREOF



(57) Abstract

Provided are purified and isolated VEGF–C polypeptides capable of binding to at least one of KDR receptor tyrosine kinase (VEGFR–2) and Flt4 receptor tyrosine kinase (VEGFR–3); analogs of such peptides that have VEGF–C–like or VEGF–like biological activities or that are VEGF or VEGF–C inhibitors; polynucleotides encoding the polypeptides; vectors and host cells that embody the polynucleotides; pharmaceutical compositions and diagnostic reagents comprising the polypeptides; and methods of making and using the polypeptides.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 98/01973

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/52 C12N15/10 C07K16/24 C12Q1/68
C12N15/62 G01N33/50 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N C12Q A01K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOUKOV V ET AL: "A NOVEL VASCULAR ENDOTHELIAL GROWTH FACTOR, VEGF-C, IS A LIGAND FOR THE FLT4 (VEGFR-3) AND KDR (VEGFR-2) RECEPTOR TYROSINE KINASES" EMBO JOURNAL, vol. 15, no. 2, 1996, pages 290-298, XP002022272 see the whole document ---	1-5,7,8, 10,11, 30-34, 37-39,54
X	LEE, J., ET AL. : "vascular endothelial growth fator-related protein: a ligand and specific activator of the tyrosine kinase receptor flt4" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 93, March 1996, pages 1988-1992, XP002066360 see the whole document ---	1-3,10, 11, 30-34, 37,38,54

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
29 May 1998	03.07.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Holtorf, S

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 39515 A (HUMAN GENOME SCIENCES INC ;ROSEN CRAIG A (US); HU JING SHAN (US);) 12 December 1996 pages 21,34; examples 2,3,4,5,6	1-3,10, 11, 30-34, 36-38, 40,54
X	LEE,J., ETAL. : "VASCULAR ENDOTHELIAL GROWTH FACTOR RELATED PROTEIN (vrp): A LIGAND AND SPECIFIC ACITVATOR OF THE TYROSINE KINASE RECEPTOR Flt4" EMBL SEQUENCE DATA LIBRARY, 10 January 1996, HEIDELBERG, GERMANY, XP002066361 ACCESSION NO. U4142	55,56
X	JOUKOV,V., ET AL. : "A NOVEL VASCULAR ENDOTHELIAL GROWTH FACTOR VEGF-C IS A LIGAND FOR THE FLT4 (VEGFR-3)AND KDR (VEGFR-2) RECEPTOR TYROSINE KINASES" EMBL SEQUENCE DATA LIBRARY, 1 February 1996, HEIDELBERG, GERMANY, XP002066362 ACCESSION NO. X94216	55,56
A	COHEN T ET AL: "VEGF121, A VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) ISOFORM LACKING HEPARIN BINDING ABILITY, REQUIRES CELL-SURFACE HEPARAN SULFATES FOR EFFICIENT BINDING TO THE VEGF RECEPTORS OF HUMAN MELANOMA CELLS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 19, 12 May 1995, pages 11322-11326, XP002061896 see the whole document	1-57
P,X	WO 97 05250 A (UNIV HELSINKI LICENSING ;ALITALO KARI (FI); JOUKOV VLADIMIR (FI)) 13 February 1997 cited in the application pages 10,13-17, 27; examples 8,9,11,14,15,19,22,27,28,29; claims	1-11, 30-34, 36-40, 43,53-56
P,X	JOUKOV,V., ET AL. : "PROTEOLYTIC PROCESSING REGULATES RECEPTOR SPECIFICITY AND ACTIVITY OF VEGF-C" THE EMBO JOURNAL, vol. 16, no. 13, June 1997, pages 3898-3911, XP002066363 see the whole document	1-5, 7-11,14, 15,20, 21, 30-34,54
3 P,X	WO 97 09427 A (GENENTECH INC) 13 March 1997 pages 3,5,9,10,11,24,25,34; example 5,7	1-3,10, 11, 30-38,54
3	-/--	

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 98/01973

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 17442 A (IMMUNEX CORP) 15 May 1997 pages 3,7,8,17,19,21,24; examples ---	1-3,10, 11, 30-34, 36-38, 40,54
P,X	ACHEN, M.G., ET AL.: "VASCULAR ENDOTHELIAL GROWTH FACTOR D (VEGF-D) IS A LIGAND FOR THE TYROSINE KINASES VEGF RECEPTOR 2 (Flk1) AND vegf RECEPTOR 3 (Flt4)" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 95, January 1998, pages 548-553, XP002066364 abstract, pages 548, right column, page 549, 551; figures 1 + 4; ---	1-3, 30-34
P,X	JELTSCH,M., ET AL. : "HYERPLASIA OF LYMPHATIC VESSELS IN VEGF-C TRANSGENIC MICE" SCIENCE, vol. 276, 30 May 1997, pages 1423-1425, XP002066365 see the whole document ---	1-3,10, 11, 30-32, 37-40, 53,54
T	JOUKOV,V., ET AL.: "A RECOMBINANT MUTANT VASCULAR ENDOTHELIAL GROWTH FACTOR-C THAT HAS LOST VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 BINDING , ACTIVATION, AND VASCULAR PERMEABILITY ACTIVITIES" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 12, 20 March 1998, pages 6599-6602, XP002066366 see the whole document -----	1-57

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INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/US 98/01973

Box I Observations where certain claims were found unsearchable (Continuati n of it m 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37-47 and 49,50,52,53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The polypeptide analog of claim 13 was searched as refering to the analog mentioned in claim 12.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/US 98/01973

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9639515 A	12-12-1996	AU 6046796 A	24-12-1996
		EP 0837934 A	29-04-1998
WO 9705250 A	13-02-1997	AU 6616996 A	26-02-1997
		EP 0842273 A	20-05-1998
WO 9709427 A	13-03-1997	AU 7012896 A	27-03-1997
WO 9717442 A	15-05-1997	AU 1116297 A	29-05-1997